Influence of Inflammation and of Stage of Lung Development on the Development of Neonatal Lung Injury

Akademisk avhandling

Som för avläggande av Medicine Doktorsexamen vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssal 1,
Drottning Silvias Barn- och Ungdomssjukhus, SU/Östra, Göteborg

fredagen 17 december 2010, kl. 13.00

av

Erica Bäckström

Fakultetsopponent: Adj. Professor Stephan Glasser,
Cinicinnati Children's Hospital Medical Center, Ohio, USA

Avhandlingen baseras på följande delarbeten:

I. Maternal IL-1b Production Prevents Lung Injury in a Mouse Model of Bronchopulmonary Dysplasia. Bäckström, E., Lappalainen, U., and Bry, K. Am J Respir Cell Mol Biol Vol 42. pp 149–160, 2010.

II. Developmental Stage is a Major Determinant of Lung Injury in a Murine Model of Bronchopulmonary Dysplasia. Bäckström, E., Hogmalm, A., Lappalainen, U., and Bry, K. Accepted, Pediatric Research, 2010.

III. Elevated Gastric Aspirate Levels of Inflammatory Cytokines at Birth Are Associated with the Development of Bronchopulmonary Dysplasia Stichel, H., Bäckström, E., Hafström, O., Nilsson, S., Lappalainen, U., and Bry, K. Submitted, Acta Pediatrica, 2010.

UNIVERSITY OF GOTHENBURG

Influence of Inflammation and of Stage of Lung Development on the Development of Neonatal Lung Injury

Erica Bäckström

Department of Pediatrics, Institute of Clinical Sciences, The Sahlgrenska Academy at the University of Gothenburg, Sweden

Abstract

Bronchopulmonary dysplasia (BPD) is a major cause of mortality and long-term morbidity in prematurely born infants. Pulmonary inflammation, and abnormal alveolar and vascular development of the lung are histological characteristics of BPD. Interleukin (IL)-1β is a central cytokine in inflammation. Increased concentration of IL-1β in amniotic fluid or postnatally in the lungs of newborn infants is associated with the development of BPD. Bitransgenic mice expressing human (h)IL-1β in the lung epithelium develop a BPD-like illness. The aims of this thesis were to study the development of hIL-1β-induced lung disease in this transgenic mouse model in order to find factors regulating the development of the disease and to analyze gastric fluid in order to identify premature infants who are at high risk of developing BPD.

Since preterm labor is often preceded by intrauterine infection, the majority of infants born at less than 30 weeks of gestation have been exposed to antenatal inflammation. To study the effect of maternal inflammation on fetal inflammatory responses, hIL-1β expression was induced in pregnant dams and their hIL-1β-expressing offspring were compared to those of control dams. In bitransgenic dams, the production of hIL-1β starts before the fetuses start producing hIL-1β. The results show that maternal hIL-1β production preceding fetal hIL-1β production causes silencing of inflammatory genes in the lungs of bitransgenic offspring and protects them against hIL-1β-induced lung injury. The mammalian lung undergoes five distinct developmental stages, the embryonic, the pseudoglandular, the canalicular, the saccular, and the alveolar stage. Children developing BPD are typically born in the early saccular stage. Expression of hIL-1β was induced in fetal and newborn mice at different time points in order to study the sensitivity of the lung to hIL-1β-induced injury during the different developmental stages. The results show that hIL-1β production in the lungs during the mid-saccular stage, but not in the late canalicular-early saccular or late saccular-alveolar stages, is sufficient to cause a BPD-like illness with abnormal lung development, inflammation, and increased mortality.

Usually tracheal aspirates are used to detect inflammation in the newborn lung. Obtaining tracheal aspirates from premature infants requires intubation, an invasive procedure that may promote the development of BPD. Gastric aspirate samples can be retrieved from premature infants at the time of routine placement of a nasogastric tube shortly after birth. The results show that levels of inflammatory proteins in the gastric aspirates are strongly increased in fetuses exposed to clinical chorioamnionitis and are associated with the development of BPD. These results suggest that gastric aspirate can be used instead of more invasive methods to assess the exposure of premature infants to inflammation and to assess the impact of perinatal inflammation on neonatal outcome.

Keywords: premature birth, BPD, inflammation, IL-1β, lung development, gastric aspirate
ISBN 978-91-628-8189-4
E-published at http://hdl.handle.net/2077/23726